



**PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

<i>In re</i> Application of:	)	
	)	
Philip A. COLE <i>et al.</i>	)	
	)	Group Art Unit: 1652
Serial No. 09/811,870	)	
	)	Examiner: D. Steadman
Filed: March 21, 2001	)	
	)	
For: <b>Bisubstrate Inhibitors of Kinases</b>	)	Atty. Dkt. No. 001107.00108

**DECLARATION UNDER RULE 132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Philip A. Cole, declare:

1. I am a named co-inventor of the subject application. I am the E.K. Marshall and Thomas H. Maren Professor and Director of the Department of Pharmacology and Molecular Sciences at The Johns Hopkins University School of Medicine, Baltimore, Maryland.

2. I am aware that the Patent and Trademark Office has rejected certain pending claims for lack of enablement of the full scope of the claims and for lack of an adequate written description of the claimed genus of bisubstrate inhibitors.

3. Five additional bisubstrate inhibitors have been made in my laboratory based on the dissociative transition state model as taught in the subject application (see paragraph 26). These inhibitors have a dimension of greater than 4.9 Angstroms

measured from a gamma phosphorous of the nucleotide or nucleotide analog moiety to the proton donor in the peptide moiety.

4. The five additional bisubstrate inhibitors are:
  - a. Src protein-ATP conjugate which inhibits Src kinase (CSK)
  - b. Np13 protein-ATP conjugate which inhibits SR protein kinase (Skylp)
  - c. peptide-ATP conjugate which inhibits cyclin dependent kinase (CDK2)
  - d. Abl kinase substrate-converted peptide-ATP conjugate which inhibits Abl kinase
  - e. Src substrate-converted peptide-ATP conjugate which inhibits Src

5. Like the inhibitors of insulin receptor kinase and protein kinase A taught in the subject application, each of these five additional bisubstrate inhibitors potently inhibits its target protein kinase enzyme.

6. Each of the five inhibitors was identical to the insulin receptor kinase bisubstrate inhibitor taught in the specification with respect to the nucleotide or nucleotide analog moiety (ATP $\gamma$ S) and the tether (acetamide group).

7. The peptide portions of each of the five inhibitors differed, providing specificity for each inhibitor.

A.	Src-protein-ATP	ECQYQPGENL	{
B.	Np13 protein-ATP	ACRERSPTR	
C.	Cdk substrate peptide-ATP	HHASPRKQGKKENGPPHSHTLKGRRLFGEDPPKE	
D.	Abl kinase substrate-converted peptide-ATP	AEEEEIFGEFEAKK	
E.	Src substrate-converted peptide-ATP	FGFEGFGEFGEFG	

8. We have also modified our original bisubstrate inhibitor of insulin receptor kinase (compound 2 in the subject application). We removed one of the phosphates of the ATP, approximating the effect of removal of the acetamide tether between the ATP and the peptide. This compound was 200-fold less potent than the parent compound.

9. These data demonstrate the importance of the tether of greater than or equal to 4.9 Angstroms. In addition, they demonstrate the broad applicability of the bisubstrate inhibitor design disclosed and claimed in the subject application. Due to the conserved features among the protein kinases of the human genome at the sequence and three-dimensional structural levels, I would expect the bisubstrate inhibitor design to work for most, if not all, of the protein kinases.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 9/29

Philip A. Cole  
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